

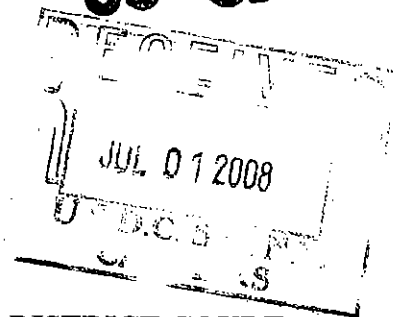
JUDGE PRESKA

08 CIV 6009

WHITE & CASE LLP

1155 Avenue of the Americas
New York, New York 10036
(212) 819-8200

*Attorneys for Plaintiff
Novartis Pharmaceuticals Corporation*



**UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK**

NOVARTIS PHARMACEUTICALS
CORPORATION

Plaintiff,

v.

ALTAIRE PHARMACEUTICALS, INC.

Defendant.

COMPLAINT

Civil Action No. _____

Plaintiff Novartis Pharmaceuticals Corporation ("Novartis"), by its attorneys White & Case LLP, for its Complaint against Defendant Altaire Pharmaceuticals, Inc. ("Altaire"), alleges:

1. This action arises out of Defendant Altaire's willful infringement of certain patents owned by Plaintiff Novartis, as well as Altaire's breach of related contractual obligations owed to Novartis.

2. Over seven years ago, Novartis affiliate CIBA Vision Corporation ("CIBA Vision") sued one of the entities for which Altaire manufactures ophthalmic products, Cynacon/OCuSOFT, Inc. ("Ocusoft"), for infringement of four patents in the United States District Court for the District of New Jersey (the "First Litigation"). Two of the four patents at issue in the First Litigation serve as bases for this Complaint (the "Novartis patents").

3. The parties to the First Litigation reached a settlement agreement, prior to trial on the merits, in which agreement Altaire and Novartis joined (the "Settlement Agreement").

4. Pursuant to the Settlement Agreement, Altaire agreed not to manufacture Ocusoft products in such fashion as would infringe the Novartis patents.

5. Upon information and belief, Altaire has resumed infringement of the Novartis patents by at least making and selling Ocusoft products in direct violation of the Settlement Agreement. Altaire has also willfully manufactured other infringing products on behalf of other entities.

THE PARTIES

6. Plaintiff Novartis Pharmaceuticals Corporation, is a corporation organized and existing under the laws of Delaware, having a principal place of business at One Health Plaza, East Hanover, NJ 07936.

7. Upon information and belief, Altaire Pharmaceuticals, Inc., is a corporation organized and existing under the laws of New York, having a principal place of business at 311 West Lane, Aquebogue, New York 11931.

JURISDICTION AND VENUE

8. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1332, 1338(a), and 1367.

9. Because Altaire is domiciled in New York, and because Altaire maintains systematic and continuous contacts with New York, including the manufacture of drug products for distribution to pharmacies and other retailers in New York, this Court has personal jurisdiction over Altaire.

10. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400.

THE NOVARTIS PATENTS

11. On March 4, 1997, the United States Patent and Trademark Office issued to Ciba-Geigy Corporation U.S. Patent No. 5,607,698 (“the ‘698 patent”), entitled “Method of Preserving Ophthalmic Solution and Compositions Therefor.” A copy of the ‘698 patent is attached hereto as Exhibit A.

12. On March 10, 1998, the United States Patent and Trademark Office issued to CIBA Vision U.S. Patent No. 5,725,887 (“the ‘887 patent”), entitled “Method of Preserving Ophthalmic Solutions and Compositions Therefor.” A copy of the ‘887 patent is attached hereto as Exhibit B.

13. The ‘698 and ‘887 patents are currently assigned to Novartis.

THE ALTAIRE PRODUCTS

14. Upon information and belief, Defendant Altaire has been and is presently making for sale or offer for sale, within this Judicial District and elsewhere in the United States, ocular lubricants, including, but not limited to, “Tears Again® Night and Day Gel” and “ECKERD Gentle™ lubricant eye drops” (the “Altaire Products”).

15. Upon information and belief, Altaire has manufactured “Tears Again® Night and Day Gel” for Ocusoft, and “ECKERD Gentle™ lubricant eye drops” for ECKERD Pharmacy.

THE FIRST LITIGATION AND ITS SETTLEMENT

16. On or about May 4, 2001, CIBA Vision brought the First Litigation, CIBA Vision Corporation v. Cynacon/Ocusoft, Inc., Civil Action No. 01-CV-2170 (AMW), in the United States District Court for the District of New Jersey.

17. By its Complaint in the First Litigation, CIBA Vision alleged, inter alia, infringement of the ‘698 and ‘887 Patents by Ocusoft.

18. On or about October 25, 2001, on behalf of itself and CIBA Vision, Novartis entered into the Settlement Agreement with Altaire, acting on behalf of itself and Ocusoft, to, inter alia, settle the First Litigation.

19. Pursuant to the Settlement Agreement, Altaire was prohibited from manufacturing, selling, or distributing ophthalmic products utilizing preservative systems other than those exhibiting particular compositional limitations.

20. Also pursuant to the Settlement Agreement, Novartis reserved the right to test products manufactured by Altaire employing ophthalmic preservative systems to ensure, inter alia, that such products do not violate the terms of the Settlement Agreement.

21. Also pursuant to the Settlement Agreement, on November 7, 2001, CIBA Vision filed a Notice of Voluntary Dismissal of the First Litigation, pursuant to Federal Rule of Civil Procedure 41(a)(1). The New Jersey District Court dismissed the First Litigation on November 9, 2001.

ALTAIRE RESUMES INFRINGEMENT

22. Novartis has tested the Altaire Products, as contemplated by the Settlement Agreement (the "Testing").

23. The Testing has revealed that the Altaire Products utilize preservative systems that exceed certain ingredient content limitations by which Altaire agreed to be bound in entering into the Settlement Agreement. The Testing has similarly revealed that, by its manufacture of the Altaire Products, Altaire itself infringes and facilitates the infringement by others of the '698 and '887 patent claims.

24. Upon information and belief, Altaire continues to manufacture and supply the Altaire Products for distribution to pharmacies and other retailers in the United States, including in this District.

COUNT I
(Patent Infringement)

25. Novartis realleges and incorporates by reference the allegations set forth in paragraphs 1-24 above.

26. Upon information and belief, the Altaire Products facilitate a method for preserving ophthalmic solutions which, under the Patent Laws of the United States, 35 U.S.C. § 271 (a)-(c), infringe the '698 patent or induce or contribute to the infringement of the '698 patent. Upon information and belief, Altaire will continue to infringe the '698 patent unless enjoined by this Court.

27. Upon information and belief, Altaire's infringement of the '698 patent is deliberate and willful.

28. Altaire's infringement of the '698 patent has damaged and continues to damage Novartis irreparably.

29. Novartis has no adequate remedy at law unless Altaire's infringing activities are enjoined by this Court.

COUNT II
(Patent Infringement)

30. Novartis realleges and incorporates by reference the allegations set forth in paragraphs 1-24 above.

31. Upon information and belief, the Altaire Products comprise ophthalmic solutions which, under the Patent Laws of the United States, 35 U.S.C. § 271 (a)-(c), infringe the '887 patent or induce or contribute to the infringement of the '887 patent.

32. Upon information and belief, Altaire will continue such infringement unless enjoined by this Court.

33. Upon information and belief, Altaire's infringement of the '887 patent is deliberate and willful.

34. Altaire's infringement of the '887 patent has damaged and continues to damage Novartis irreparably.

35. Novartis has no adequate remedy at law unless Altaire's infringing activities are enjoined by this Court.

COUNT III
(Breach of Contract)

36. Novartis realleges and incorporates by reference the allegations set forth in paragraphs 1-24 above.

37. Despite its contractual obligations under the Settlement Agreement, Altaire manufactured and/or distributed products, including the Altaire Products, utilizing preservative systems having an ingredient content that is prohibited under the terms of the Settlement Agreement.

38. Altaire's manufacture and/or distribution of various products, including the Altaire Products, constitutes breach of the Settlement Agreement.

39. As a direct and proximate result of Altaire's breach of the Settlement Agreement, Novartis has suffered and continues to suffer damages, and is entitled to specific performance by Altaire of its obligations thereunder.

PRAYER FOR RELIEF

Wherefore, Plaintiff Novartis Pharmaceuticals Corporation prays for a judgment in its favor against Defendant Altaire Pharmaceuticals, Inc., as follows:


- A. That Altaire has infringed the '698 and '887 patents;
- B. That Altaire, its officers, agents, attorneys, servants, successors, assigns, employees, and all those in privity or in active concert and participation with Altaire, are preliminarily and permanently enjoined from infringing the '698 and '887 patents, or inducing or contributing to the infringement of the '698 and '887 patents for the remainder of their terms;
- C. Entering judgment for Novartis on Count III of this Complaint;
- D. Awarding Novartis damages, together with interest, to compensate it for Altaire's breach of the Agreement;
- E. Directing Altaire specifically to perform its obligations under the Settlement Agreement;
- F. That Altaire's infringement is willful and increasing the damages award to Novartis up to three times, pursuant to 35 U.S.C. § 284;
- G. That this is an exceptional case, under 35 U.S.C. § 285, and awarding Novartis its reasonable attorneys' fees, costs, and expenses; and
- H. Awarding Novartis such other and further relief as this Court may deem just and proper.

Dated: July 1, 2008
New York, New York

Respectfully submitted,

WHITE & CASE LLP

1155 Avenue of the Americas
New York, New York 10036
Phone: (212) 819-8200
Facsimile: (212) 354-8113

By: 
Jeffrey J. Oelke (JO 2534)
James S. Trainor, Jr. (JT 2520)
Amit H. Thakore (AT 8098)

*Attorneys for Plaintiff Novartis
Pharmaceuticals Corporation*

EXHIBIT A

United States Patent

Martin et al.

[19]

[11] Patent Number: 5,607,698

[45] Date of Patent: Mar. 4, 1997

[54] METHOD OF PRESERVING OPHTHALMIC SOLUTION AND COMPOSITIONS THEREFOR

[75] Inventors: Stephen M. Martin, Roswell; Fu-Pao Tsao, Lawrenceville, both of Ga.

[73] Assignee: Ciba-Geigy Corporation, Tarrytown, N.Y.

[21] Appl. No.: 339,447

[22] Filed: Nov. 14, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 99,986, Jul. 29, 1993, abandoned, which is a continuation of Ser. No. 968,224, Oct. 29, 1992, abandoned, which is a continuation of Ser. No. 733,485, Jul. 22, 1991, abandoned, which is a continuation of Ser. No. 376,083, Jul. 6, 1989, abandoned, which is a continuation-in-part of Ser. No. 229,163, Aug. 4, 1988, abandoned.

[51] Int. Cl.⁶ A61K 33/40

[52] U.S. Cl. 424/613; 514/714; 514/839; 514/840

[58] Field of Search 514/714, 839, 514/840; 424/613

References Cited

U.S. PATENT DOCUMENTS

3,701,825 10/1972 Radimer et al. 423/273
4,051,058 9/1977 Böwing et al. 252/186.31
4,294,575 10/1981 Kowalski 8/111

4,304,762 12/1981 Leigh 423/272
4,347,149 8/1982 Smith et al. 252/102
4,350,681 9/1982 Fulton 424/53
4,614,646 9/1986 Christiansen 423/272
4,743,447 5/1988 Le Ronzic et al. 424/130
4,812,173 3/1989 Tsao et al. 423/272
4,889,689 12/1989 Tsao 422/30

FOREIGN PATENT DOCUMENTS

15818 9/1980 European Pat. Off.
1382466 1/1975 United Kingdom
1500707 2/1978 United Kingdom

OTHER PUBLICATIONS

Contacto, International Contact Lens Journal, vol. 23, No. 1, Jan. 1979, pp. 37-40.
American Journal of Optometry and Physiological Optics, vol. 65, No. 2, pp. 91-98, Feb. 1988.
Kontaktlinsen-Chemie, Merian Verlag 1984, p. 173.

Primary Examiner—Zohreh Fay

Attorney, Agent, or Firm—Norbert Gruenfeld

[57] ABSTRACT

A preservative for ophthalmic solutions having an active ingredient is provided, having a hydrogen peroxide content of about 0.001% to about 0.10% by weight; and diethylene triamine penta(methylene phosphonic acid) or a physiologically compatible salt thereof, present at about 0.002% to 0.03% by weight and/or 0.005% to about 0.20% by weight of 1-hydroxyethylidene-1,1-diphosphonic acid, or physiologically acceptable salt thereof.

28 Claims, No Drawings

5,607,698

1

METHOD OF PRESERVING OPHTHALMIC SOLUTION AND COMPOSITIONS THEREFOR

This application is a continuation of application Ser. No. 08/099,986 filed Jul. 29, 1993 now abandoned, which is a continuation of application Ser. No. 07/968,224 filed Oct. 29, 1992 now abandoned, which is a continuation of application Ser. No. 07/733,485 filed Jul. 22, 1991 now abandoned, which is a continuation of application Ser. No. 07/376,083 filed Jul. 6, 1989 now abandoned, which is continuation-in-part of application Ser. No. 07/229,163 filed Aug. 4, 1988 now abandoned.

The present invention relates to a method of preserving ophthalmic solutions with trace amounts of stabilized peroxy compounds. More particularly, this invention relates to the use of stabilized trace amounts of hydrogen peroxide as preservative in buffered saline for eye care solutions.

Hydrogen peroxide is a well-known germicidal agent. For example, hydrogen peroxide in the form of a relatively dilute solution, e.g. about 0.5 to 6% by weight in water, is known to be effective as a disinfectant for use with contact lenses in order to kill any contaminating microorganisms.

One drawback with unstabilized dilute hydrogen peroxide solutions, however, is that without the use of a stabilizer or a combination of stabilizers, the aqueous peroxide solutions characteristically decompose over a period of time. The rate at which such dilute hydrogen peroxide solutions decompose will, of course, be dependent upon such factors as pH and the presence of trace amounts of various metal impurities, such as copper or chromium, which may act to catalytically decompose the same. Moreover, at moderately elevated temperatures, the rate of decomposition of such dilute aqueous hydrogen peroxide solutions is greatly accelerated.

A large variety of stabilizers have been proposed for use with hydrogen peroxide to deactivate trace catalytic impurities, including stannous salts, ethylene diamine tetra acetic acid, and the like. For example, U.S. Pat. No. 3,860,391 discloses bleaching compositions containing hydrogen peroxide and, as a stabilizer, amino lower alkylene phosphates, including diethylene triamine penta(methylene phosphonic acid) or salts thereof, and/or hydroxy alkane phosphates, with or without additional stabilizer constituents, and adjusted to a pH of between about 9.0 and 12.0 with, e.g. sodium hydroxide, for the bleaching of cellulosic materials. Exemplified are compositions having a pH of 12.0. However, such highly basic compositions are undesirable in ophthalmically-related solutions, including eyewashes and contact lens cleaning solutions.

Also, British Patent No. 1,500,707 discloses a contact lens sterilizing solution using hydrogen peroxide with 200-2000 ppm of a phosphate [pyrophosphate] stabilizer at a pH of 4.5.

However, the disinfection is not carried out at a pH consistent with the ocular environment since the pH needs to be elevated to around 7. Also, the peroxide must be eliminated so as to make the solution compatible with the eye.

U.S. Pat. No. 4,304,762 discloses stabilization of aqueous hydrogen peroxide by addition of diethylenetriamine penta(methylene phosphonic acid) or a salt thereof at a pH of about 7. However, the stabilizing phosphonate compound is reported to be particularly effective for use with alkaline hydrogen peroxide solutions. Further these solutions are disclosed as being of use as a base for liquid bleach products. There is neither any hint that trace amounts of hydrogen peroxide are effectively stabilized nor is there any indication

2

that hydrogen peroxide might be used as a preservative for an ophthalmic solution.

Some of the eye care solutions commercially available today use benzalkonium chloride, rather than hydrogen peroxide, as a preservative. For example, contact lens solutions typically contain 0.9% sodium chloride, buffers, surfactants, wetting agents, and 0.002 to 0.01% benzalkonium chloride. Benzalkonium chloride is also used in other products, including isotonic decongestant ophthalmic solutions, such as Visine® eyedrops manufactured by the Leeming Division of Pfizer, Inc.

A problem exists, however, in that benzalkonium chloride, being cationic in character, reacts with proteins found in the ocular environment and causes unwanted deposits on soft contact lenses. Benzalkonium chloride and its analogs are also taken up by lens material and can have a deleterious effect on the structure of the lens [Davis, S. S. et al., "The Adsorption of Cationic Antimicrobial Agent Onto Poly-Hema", Colloids and Surfaces, 12, 203-212 (1984)]. In addition, benzalkonium chloride is inactivated by many compounds, including those associated with cotton and nylon fibers. Furthermore, in Swan, K. C., "Reactivity of the Ocular Tissues to Wetting Agents", Am. J. Ophthalmol., 27, 118 (1944), it was noted that repeated use of benzalkonium chloride at concentrations of 1:5000 or stronger can denature the corneal protein and cause irreversible damage. It was also found that 0.04% to 0.05% solutions of benzalkonium chloride can cause superficial puncture disturbance of the corneal epithelium.

Other preservatives currently in use include thimerosal, which can cause a sensitivity reaction to the eye, and sorbic acid, which commonly causes lens discoloration. The disadvantages of the commonly used preservatives such as thimerosal, benzalkonium chloride and others are discussed in the following literature: M. Sibley, et al., "Understanding Sorbic Acid-Preserved Contact Lens Solutions", International Contact Lens Clinic, 11 (9), 531 (1984); M. Orton, et al., "Measurement of Preservative Binding with Soflens® (polymacon) Contact Lens", Aust J Optom., 59, 277 (1976); and M. Akers, "Consideration in selecting antimicrobial preservative agents for parenteral product development", Pharmaceutical Technology, May, p. 36 (1984).

OBJECTS OF THE INVENTION

An object of the invention is to provide a preservative for all manner of ophthalmic and ophthalmically related solutions having hydrogen peroxide compatible components which does not suffer from the aforementioned defects.

Another object of the invention is to provide preserved ophthalmic and ophthalmically related solution formulations which are free of the known art preservatives.

Yet another object of the invention is to provide a means of preserving ophthalmic and ophthalmically related solutions with hydrogen peroxide or hydrogen peroxide generating components.

SUMMARY OF THE INVENTION

Surprisingly, the disadvantages of the prior art preservatives are overcome by stabilized trace peroxy compounds provided by the present invention which may be used as a preservative in ophthalmic solutions such as eye lubrication solutions, ophthalmic drug formulations and contact lens solutions.

5,607,698

3

The low levels of peroxy compounds are below the commercially suitable amounts necessary for the peroxy compound to act as a disinfectant and is either low enough to be tolerable to direct application to the eye or may be made so by simple dilution with water or saline. In addition, the pH is also compatible with the ocular environment or upon the dilution indicated above is made so. For ophthalmic solutions (those which are to be instilled in the eye directly), the peroxy content and pH must per se be in the "ocular compatible range". Ophthalmic related solutions (those which are used in conjunction with contact lenses, other than "comfort or lubricating" drops which may be for instillation directly to the eye) may have appreciably higher peroxy content, but are intended to be diluted before being instilled in the eye or are used in such small amounts in the eye, that natural tear fluid dilution is sufficient to convert that solution to a solution which is compatible with the ocular environment.

The invention therefore relates to hydrogen peroxide or a source of hydrogen peroxide in trace amounts as a preservative for an ophthalmic solution, said hydrogen peroxide being especially effectively stabilized by addition of diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonate, to the use of said stabilized trace amounts of hydrogen peroxide for preserving an ophthalmic solution, to ophthalmic solutions so preserved, to the manufacture of so preserved ophthalmic solutions and to a method of preserving any ophthalmic solution by adding thereto said stabilized trace amounts of stabilized hydrogen peroxide or a source of hydrogen peroxide.

For example, the trace amount of the hydrogen peroxide in these ophthalmic solutions ranges from about 0.001% (10 ppm) to about 0.10% (1000 ppm) by weight and is stabilized by about 0.002% (20 ppm) to about 0.03% (300 ppm) by weight of diethylene triamine penta(methylene phosphonic acid) or a physiologically compatible salt thereof.

Alternatively or additionally from 0.005% to about 0.2% by weight of 1-hydroxyethylidene-1,1-diphosphonic acid and/or from about 0.005% to about 0.1% of glycerin can be added to the solution.

DESCRIPTION OF THE INVENTION

Trace amounts of peroxy compounds stabilized with a hydrogen peroxide stabilizer, especially diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid may be utilized as a preservative for drugs, eyewashes, or other solutions containing an active ingredient designed to be used in the ocular environment. The preservative according to the present invention may be used in the ocular environment. The preservative according to the present invention may be used in any ophthalmic solution as long as the active ingredient in that solution is compatible with trace amounts of the peroxy compounds. Also, virtually any peroxy compound may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. EXAMPLES of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, cannot be stabilized utilizing the present system.

The full scope of the present invention includes ophthalmic active agent containing solutions as well as solutions which are ophthalmic active agent free. The former group

4

contains at least one medicinal agent for application directly to the eye. The latter group comprises such solutions as preserved saline, preserved contact lens cleaning solutions, preserved contact lens stabilizing solutions, preserved wetting solutions, and preserved lubricating solutions, among others.

It is believed that most compounds, when preserved by the present invention, are compatible with trace amounts of hydrogen peroxide. The following is a non-exhaustive, non-limiting, illustrative list of active ingredients and excipients that are compatible with the preservative according to the present invention: atropine, homatropine, cyclopentolate, tropicamide, lachesine, dibutolone, oxyphe-nonium, eucatropine, ephedrine, carbachol, methacholine, pilocarpine hydrochloride, isofluorophate, physostigmine, neostigmine, lignocaine, cocaine, acetylcholine chloride, antazoline phosphate, betaxolol hydrochloride, demecarium bromide, dipivefrin hydrochloride, erythromycin, gentami-cin sulfate, homatropine hydrobromide, idoxuridine, isosor-bide, lanolin, naphazoline hydrochloride, neomycin sulfate, pheniramine maleate, polysorbate gelatin (Tween), pyrri-amine maleate, scopolamine hydrobromide, hyaluronic acid, sodium hyaluronate, tetracaine hydrochloride, oxmetazolin, tetrahydrozoline hydrochloride, diclofenac sodium, dextran, carteolol, sulfanilamide, procaine, proparacaine hydrochlo-ride, sulfisoxazole disolamine, indomethacin, clonidine, corynanthine, arachidonic acid, linoleic acid, H-thymidine and 3H-thymidine, inositol triphosphate, inositol phos-phates, phosphatidylinositol and phosphatidylinositol phos-phates.

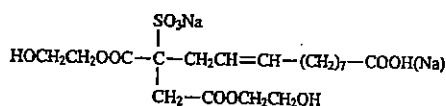
Excipients of various types compatible with the present invention include, but are not limited to:

- Polysorbate gelatin (Tween)
- Dextran
- Linolin
- Inositol phosphates
- Alkylsulfosuccinates
- Sulfosuccinamate
- Alkyl Silicone Sulfosuccinates
- Alkylpolyether carboxylates
- Alkylaryl polyethoxylamines
- Alkylarylsulfonates
- Alpha Olefin sulfonates
- Alkyl surfates
- Alkyl ether sulfates
- Alkanol amides and alkamides
- Alkylamphoterics
- Amphoterics based on Alkyl imidazoline
- Betaines
- Alkylaminopropionates
- Alkyliminodipropionates
- Alkylamphoglycinates
- Alkylamphocarboxyglycinates
- Alkylamphocarboxyptopinatates
- Alkylamphopropionates
- Alkylamidopropylhydroxysultaines
- Alkyletherhydroxypropylsultaines
- Alkylamphopropylsulfonates
- Quaternary ammonium polymers
- Quaternary ammonium halides
- Polyacrylamide

5,607,698

5

Polyacrylates
 Polyvinyl pyrrolidone
 Polyvinyl alcohol
 Alkylalcohol ethoxylates
 Hydroxyalkylcelluloses
 Alkylamidopropyl PG-Dimonium chloride phosphates
 Alkylampho PG-glycinate phosphates
 Glyceryl monoalkylates
 Sorbitan alkylates (span)
 Pluronics
 Tetronics
 Sodium alkyl sulfates
 Sodium Butoxyethoxy Acetate
 Phosphate esters
 Glycosides
 Polyglycosides
 Mannitol
 Sorbitol
 Polyoxyethylene alkyl ethers
 Grillosan having the formula

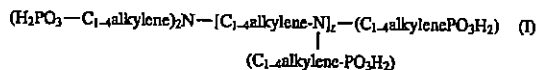


Guar gum
 Sodium hyaluronate
 Polyoxyl 40 stearate
 Polyoxylalkylene dimethylpolysiloxane

However, compounds having non-hindered hydroxyl groups attached to an aromatic ring, such as ketones and alcohols, or having a mercapto group, thioether, acetamido group, or aldehyde group will typically not be compatible. Such compounds believed not compatible with trace stabilized hydrogen peroxide include: noradrenaline, adrenaline, phenylephrine hydrochloride, amethocaine, oxybuprocaine, proxymethacaine, cromolyn sodium, benoxinate hydrochloride, chloramphenicol, chlortetracycline hydrochloride, dexamethasone, dichlorophenamide, echotioph ate iodide, epinephrine bitartrate, fluorometholone, gramicidin, hydrocortisone, methazolamide, natamycin, prednisolone acetate, sulfactamide (N¹-acetylsulfanilamide), tetracycline hydrochloride and timolol maleate.

The peroxy stabilizer used in the present invention may be any of the known stabilizers of peroxy compounds including phosphonates, phosphates, stannates, etc. However, physiologically compatible salts of phosphonic acids are preferred. Within this preferred group are

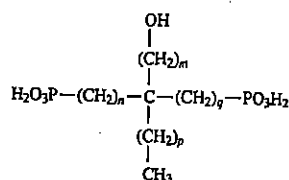
(a) compounds of the formula



wherein z is an integer of from 0-3; and

6

(b) compounds of the formula



wherein each of n, m, p and q is independently 0-4, or physiologically compatible salts thereof. Highly preferred within formula I are compounds wherein z is 2 and compounds wherein each C₁₋₄ alkylene group is C₁ or C₂. Most preferred within formula I is diethylene triamine penta(methylene-phosphonic acid) and the physiologically compatible salts thereof, marketed by Monsanto under the name Dequest® 2060. Highly preferred within formula II are compounds wherein n, m, p and q are each 0 or 1, most preferably zero, or a physiologically compatible salt thereof, marketed by Monsanto under the name Dequest® 2010.

Physiologically compatible salts of the compounds of formulae I and II include, for example, water soluble salts with conventional pharmaceutically acceptable cationic moieties, including the alkali metal, e.g. sodium, potassium, alkaline earth metal, e.g. calcium, ammonium and amine cations. Suitable amine salts include, for example, mono-, di-, and tri-lower alkyl amines, e.g. methylamine, ethylamine, diethylamine, triethylamine, dimethylamine, trimethylamine, propylamine, and the like; and mono-, di-, and tri-lower hydroxyalkyl amines, e.g. ethanolamine, diethanolamine, triethanolamine, glucamine, 2-hydroxypropylamine, and the like. By "lower" in the context of an alkyl group is meant an alkyl group having up to 6 carbon atoms, preferably up to 4 carbon atoms.

If desired, additional conventional stabilizers may be employed in conjunction with those of formulae I or II or combinations thereof in accordance with the present invention. Suitable conventional stabilizers include: water soluble stannates, such as an alkali metal or ammonium stannate, for example sodium stannate, alone or in combination with a water soluble phosphate, polyphosphate or etaphosphate salt, such as an alkali metal or ammonium salt thereof; or an amino polycarboxylic acid chelating agent, such as ethylene diamine tetraacetic acid, nitrilo triacetic acid or a water soluble salt thereof, such as an alkali metal or ammonium salt, especially the sodium salt, or mixtures thereof.

Still further peroxy stabilizers which may be used in the invention include a peroxide stabilizer selected from glycerin, polyvinyl alcohol having a molecular weight in the range of about 5,000 to about 150,000 (as long as water soluble) and being at least 80% hydrolized, propylene glycol, polyacrylic acid having a molecular weight of about 2,000 to about 100,000, diethylene glycol, and sodium hexamethaphosphate sodium polyphosphate (available from FMC under the name Hexaphos®).

The above stabilizers can be used in almost all indications previously mentioned to which the invention is applicable. However, when the solution is to come in contact with a hydrogel soft contact lens, stannate stabilizers are to be avoided as they tend to "cloud" the lens material.

Preferably, the concentration of the stabilizer of formula I or salt thereof is present in the stabilized composition in an amount between about 0.006 and about 0.02% by weight of the composition, and most preferably between about 0.006 and about 0.0120% by weight of the composition.

The stabilizer of formula II is present per 100 g of solution in an amount of at least about 0.024 m mole (50 ppm),

5,607,698

7

preferably 0.039 m mole (80 ppm) up to about 0.34 m mole (700 ppm) more preferably 0.049 m mole (100 ppm) up to about 0.29 m mole (600 ppm), most preferably 0.073 m mole (150 ppm) to about 0.19 m mole (400 ppm). The amounts in parentheses are for Dequest® 2010 which has a molecular weight of 206. Other stabilizers of formula II should be present in molar equivalents thereto.

The stabilizers other than those of formula I and II are employed in a physiologically tolerable amount, e.g. about 20 ppm to about 1000 ppm, preferably in an amount of at least 0.054 m mole (50 ppm), more preferably 0.087 m mole (80 ppm) to about 1.09 m mole (1000 ppm), still more preferably from about 0.109 m mole (100 ppm) to about 0.87 m mole (800 ppm), most preferably about 0.22 mmole (200 ppm) to about 0.65 m mole.

The pH of the stabilized solution is between about 5.5 and about 8. Preferably, the pH of the stabilized hydrogen peroxide solution is between about 6.0 and 8.0, most preferable between about 6.5 and 7.5. The pH can be adjusted as desired by incorporation of suitable amounts of acid or base of a physiologically tolerable nature in the amounts employed, e.g. hydrochloric acid and sodium hydroxide.

The pH of the stabilized solution presents another advantage over the prior art since the pH's of most existing ophthalmic solutions containing hydrogen peroxide are relatively low. The pH values of available hydrogen peroxide products for contact lenses are listed as follows:

Name of the Product	pH	% of H ₂ O ₂
AOSept (CIBA Vision)	6.3-6.6	3.3-3.5
Lensept (CIBA Vision)	3.98	3.4
Oxysept (Allergan)	3.28	3.3
Mirasept (Coopersvision)	3.96	3.6
Quiksept (Bausch & Lomb)	3.57	3.5
Puressept (Abbott Labs)	3.83	3.4
Softmate II (Barnes Hind)	3.5-3.6	3.5

Also, there may be present in the stabilized hydrogen peroxide solution according to the present invention one or more conventional, substantially inert, physiologically acceptable tonicity enhancing agents. Suitable such agents include, for example, alkali metal halides, phosphates, hydrogen phosphate, and borates. Preferred are sodium chloride, sodium phosphate monobasic and sodium phosphate dibasic. The function of such tonicity enhancing agents is to assure approximate physiologic tonicity to the solution which is instilled in the eye or to help assure such tonicity upon dilution if dilution is necessary prior to contact with the eye due to peroxide content as indicated above.

Preferably sufficient tonicity enhancing agents are present in the solution so that it is substantially isotonic or, such that, upon decomposition or dilution of the hydrogen peroxide therein, the resulting solution is substantially isotonic, e.g. substantially equivalent in tonicity to a 0.9% by weight aqueous sodium chloride solution.

A further optional ingredient is a thickener or viscosity enhancing agent. Any of the substances known in these categories which are ocularly acceptable can be used. Typical suitable thickeners include, inter alia, polyvinylalcohol, hydroxy ethylcellulose, etc. Thickeners may be present in any amount up to an amount sufficient to raise the overall solution viscosity to about 1000 cps, preferably to not more than 100 cps.

In general, the stabilized hydrogen peroxide solutions of the present invention are characterized by their extraordinary stability, even under accelerated conditions, for example by heating the solutions to 100° C. for 24 hours.

8

Thus, the shelf life of these compositions is enhanced. Moreover, the instant compositions are characterized by either physiological tolerability subsequent to hydrogen peroxide decomposition.

Another advantage in using hydrogen peroxide in ophthalmic solutions is that the trace amount of hydrogen peroxide, especially less than 100 ppm, is destroyed once it comes in contact with the eye. For example, catalase existing in the eye tissue will cause the breakdown of the hydrogen peroxide into water and oxygen. As a result, the solution, upon application, becomes preservative free and greatly minimizes adverse reactions. The problems associated with other preservatives, such as the inability to break down innocuous compounds, are eliminated.

Formulation of the solutions of the invention can be made in any conventional manner. For example, all of the components other than the hydrogen peroxide and water can be placed in a container and fresh, preferably concentrated, hydrogen peroxide added thereto with mixing. Alternatively the dry components can be rubbed up with a small portion of liquid stabilizer, then the remainder of the stabilizer added, followed by the hydrogen peroxide, and most of the water. The viscosity enhancing agent, i.e. thickener, can then be added or the formed solution can be added to the thickener. One of ordinary skill in the art will be aware of numerous variations in the manner of formulating the solutions of the invention.

When it is desirable to "neutralize" the peroxide activity, any means known, such as rinsing, contacting the solution with platinum, catalase, or any other substance known to decompose hydrogen peroxide, will suffice. Additional physiological compatible peroxide neutralizing agents include reducing agent such as pyruvic acid and suitable salts thereof such as the sodium salt.

The following examples are presented for illustrative purposes and are not intended to limit the scope of this invention, but to demonstrate the stability of the peroxy solutions as stabilized in accordance with the present invention. All parts are by weight unless otherwise indicated.

EXAMPLE 1

Dissolve 0.610 g of sodium chloride, 0.005 g of sodium tetraborate.10 H₂O, 0.5 g of boric acid, 0.006 g of diethylene triamine penta(methylene phosphonic acid) and 0.1 g of tetrahydrozoline hydrochloride in 80 ml of purified deionized water. Add 0.0225 g of sodium perborate, add water up to 100 ml and adjust the pH to 7 by the addition dropwise of dilute hydrochloric acid or sodium hydroxide. The resulting solution is then heated to 100° C. for a period of 24 hours. The solution possesses a "hot stability" of above 90%, which is the ratio of the hydrogen peroxide present in the after-heated sample to the before-heated sample, multiplied by 100[%].

EXAMPLE 2

The procedure of example 1 is duplicated, except that 0.1 g of sodium [o-[(2,6-dichlorophenyl)amino]phenyl]acetate replace the tetrahydrozoline hydrochloride. The hot stability is found to be 91.0%.

EXAMPLE 3

The procedure of example 1 is duplicated, except that 0.5 g of pilocarpine hydrochloride replace the tetrahydrozoline hydrochloride. The hot stability is found to be 74.3%.

5,607,698

9

EXAMPLE 4

The procedure of example 1 is duplicated, except that 0.1 g of naphazoline hydrochloride replace the tetrahydrozoline hydrochloride. The hot stability is found to be 81.3%.

EXAMPLE 5

Dissolve 0.61 g of sodium chloride, 0.50 g boric acid, 0.005 g of sodium borate decahydrate, 0.05 g Grillosan (from RITA), and 0.006 g diethylene triamine penta(methylene phosphonic acid) in 80 ml of deionized water. Add 0.0238 g sodium perborate. Add water up to 100 ml and adjust the pH to 7 by the addition dropwise of diluted hydrochloric acid or sodium hydroxide. The resulting solution is then heated to 100° C. for 24 hours. The hot stability of this solution is 93.1%.

EXAMPLE 6

The procedure of example 5 is duplicated except that the 0.05 g of Grillosan are replaced by 0.5 g propylene glycol. The hot stability of this solution is above 92%.

EXAMPLE 7

The procedure of example 5 is duplicated except that the 0.05 g of Grillosan are replaced by 0.5 g glycerin and an additional 0.01 g magnesium chloride. The hot stability of this solution is above 94%.

EXAMPLE 8

The procedure of example 5 is duplicated except that the 0.05 g of Grillosan are replaced by 0.1 g magnesium chloride. The hot stability of this solution is above 96%.

EXAMPLE 9

The procedure of example 5 is duplicated except that the 0.05 g of Grillosan are replaced by 0.5 g SIPEX EST-30 (sodium trideceth sulfate, CAS No. 68585-34-2, from Alcolac). The hot stability of this solution is above 92%.

EXAMPLE 10

The procedure of example 5 is duplicated except that the 0.05 g of Grillosan are replaced by 0.5 g Pluronic F-127 (BASF). The hot stability of this solution is above 93%.

EXAMPLE 11

Dissolve 0.35 g of sodium chloride, 0.35 g of potassium chloride, 0.58 g boric acid, 0.005 g sodium borate decahydrate and 0.006 g diethylene triamine penta(methylene phosphonic acid) in 80 ml of deionized water. Add 0.0238 g sodium perborate. Add water up to 100 ml and adjust the pH to 7 by the addition dropwise of diluted hydrochloric acid or sodium hydroxide. The hot stability of this solution is above 91%.

EXAMPLE 12

The procedure of example 11 is duplicated except that the 0.35 g of potassium chloride are replaced by 0.35 g of calcium chloride. The hot stability of this solution is above 93%.

10

EXAMPLE 13

The procedure of example 6 is duplicated except that the 0.5 g propylene glycol and 0.0238 g sodium perborate are replaced by 1g propylene glycol and 0.0476 g sodium perborate. The hot stability of this solution is above 98%.

EXAMPLE 14

The procedure of example 13 is duplicated except that the 1g propylene glycol is replaced by 0.1 g of citric acid. The hot stability of this solution is above 94%.

EXAMPLE 15

Dissolve 0.61 g of sodium chloride, 0.50 g boric acid, 0.005 g sodium borate decahydrate and 0.006 g diethylene triamine penta(methylene phosphonic acid) in 80 ml of deionized water. Add 0.0133 g sodium peroxide (from Mallinckrodt Cat. No. 7864). Add water up to 100 ml and adjust the pH to 7 by the additional dropwise of diluted hydrochloric acid or sodium hydroxide. The hot stability of this solution is above 93%.

EXAMPLE 16

The procedure of example 15 is duplicated except that the 0.0133 g sodium peroxide are replaced by 0.0138 g of urea hydrogen peroxide (from Aldrich Cat. No. 28913-2). The hot stability of this solution is above 53.6%.

EXAMPLE 17

Dissolve 0.61 g of sodium chloride, 0.50 g boric acid, 0.005 g sodium borate decahydrate, 0.1 g sulfanilamide (Sigma Cat. No. S-9251) and 0.006 g diethylene triamine penta(methylene phosphonic acid) in 80 ml of deionized water. Add 0.0238 g sodium perborate. Add water up to 100 ml, and adjust the pH to 7 by the addition dropwise of diluted hydrochloric acid or sodium hydroxide. The hot stability of this solution is above 92%.

EXAMPLE 18

Dissolve 0.61 g of sodium chloride, 0.50 g boric acid, 0.005 g sodium borate decahydrate, and various amounts of 1-hydroxyethylidene-1,1-diphosphonic acid in 80 ml of deionized water. Add 0.0238 g sodium perborate. Add water up to 100 ml and adjust the pH to 7 by the addition dropwise of diluted hydrochloric acid or sodium hydroxide. The hot stabilities of those solutions are listed as follows:

1-Hydroxyethylidene-1,1-diphosphonic acid (g)	Hot Stability %
0.03	87.1
0.05	90.3
0.08	96.8

EXAMPLE 19

This is an example of 1-hydroxyethylidene-1,1-diphosphonic acid as a stabilizer. The procedure of example 18 is duplicated except that various amounts of glycerin are added. The hot stabilities of these solutions are listed as follows:

5,607,698

11

1-Hydroxyethylidene-1,1-diphosphonic acid (g)	Glycerin (g)	Hot Stability %
0.03	0.03	90.3
0.05	0.03	93.5
0.08	0.03	93.5
0.03	0.05	90.3
0.05	0.05	90.3
0.08	0.05	93.5

EXAMPLE 20

The procedure of example 17 is duplicated except that the 0.1 g sulfanilamide are replaced by 0.1 g hyaluronic acid (from *Streptococcus Zooepidermicus*). The hot stability of this solution is about 86%.

EXAMPLE 21

The procedure of example 20 is duplicated except that the 0.1 g hyaluronic acid (from *Streptococcus Zooepidermicus*) are replaced by 0.1 g hyaluronic acid (from Rooster Comb.). The hot stability of this solution is above 96%.

EXAMPLE 22

The procedure of example 20 is duplicated except that the 0.1 g hyaluronic acid are replaced by 0.1 g sodium hyaluronate. The hot stability of this solution is above

EXAMPLE 23

The procedure of example 22 is duplicated except that the 0.1 g sodium hyaluronate are replaced by 0.025 g oxymetazoline. The hot stability of this solution is above 87%.

EXAMPLE 24

Microbial preservative effectiveness test results of 50 ppm hydrogen peroxide in a borate buffer are listed as follows:

PRESERVATIVE EFFECTIVENESS TEST (50 ppm H ₂ O ₂ solution)				
Challenge Microbe	Original Inoculum	Day 7	Day 14	Rechallenge on Day 14 with Inoculum
<i>E. coli</i>	1.67×10^6	Zero	Zero	1.60×10^5
<i>P. aeruginosa</i>	2.04×10^6	Zero	Zero	1.94×10^5
<i>S. aureus</i>	1.09×10^6	1.75×10^2	Zero	1.74×10^5
<i>A. niger</i>	1.46×10^5	2.15×10^4	8.40×10^3	1.00×10^5
<i>C. albicans</i> No. 1	1.63×10^6	8.00×10^2	2.40×10^2	1.41×10^5
<i>C. albicans</i> No. 2	1.63×10^6	1.35×10^3	3.40×10^2	1.41×10^5
<i>C. albicans</i> No. 3	1.63×10^6	1.75×10^3	4.90×10^2	1.41×10^5
Challenge Microbe	Day 21	Day 28	% Reduction	Pass/Fail
<i>E. coli</i>	Zero	Zero	100%	Pass
<i>P. aeruginosa</i>	Zero	Zero	100%	Pass
<i>S. aureus</i>	Zero	Zero	100%	Pass
<i>A. niger</i>	4.65×10^4	4.50×10^4		Pass
<i>C. albicans</i> No. 1	1.09×10^5	3.90×10^4		Pass
<i>C. albicans</i> No. 2	1.12×10^5	3.55×10^4		Pass
<i>C. albicans</i> No. 3	1.26×10^5	3.40×10^4		Pass

What is claimed is:

1. A method of preserving an eye wetting solution, an eye lubrication solution or an ophthalmic drug formulation comprising an ophthalmic active agent which is compatible with

12

hydrogen peroxide, said method comprising the addition to said ophthalmic solution of

(a) a source of hydrogen peroxide in sufficient amount to provide hydrogen peroxide in a trace amount from about 0.001% to about 0.01% by weight; and of

(b) one or more ocularly compatible hydrogen peroxide stabilizers in a sufficient amount to stabilize the resultant hydrogen peroxide;

said resulting peroxide preserved eye wetting solution, eye lubrication solution or ophthalmic drug formulation to be directly instilled in the eye of a mammal, and having an ocularly compatible pH of between about 5.5 and about 8.0.

2. The method of claim 1, wherein said hydrogen peroxide source is selected from the group consisting of hydrogen peroxide, sodium perborate, sodium peroxide and urea peroxide.

3. The method of claim 1 wherein said stabilizer is diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid or a physiologically compatible salt thereof.

4. The method of claim 3 wherein said effective amount of diethylene triamine penta(methylene phosphonic acid), or a physiologically compatible salt thereof, is from 0.002% to 0.03% by weight and said effective amount of 1-hydroxyethylidene-1,1-diphosphonic acid or physiologically compatible salt thereof is from 0.005% to 0.2% by weight.

5. The method of claim 1, wherein said resultant amount of hydrogen peroxide is from 0.001% to 0.01% by weight and said effective amount of diethylene triamine penta(methylene phosphonic acid), or a physiologically compatible salt thereof, is from 0.002% to 0.03% by weight.

6. The method of claim 4 wherein said stabilizer is 1-hydroxyethylidene-1,1-diphosphonic acid.

7. The method of claim 6, and further comprising adding an effective amount of glycerin.

8. The method of claim 4 wherein said stabilizer is diethylenetriamine penta(methylene phosphonic acid).

9. The method of claim 7, wherein said glycerin is added in an amount from 0.003% to 0.1% by weight.

10. The method of claim 5, and further comprising adding an effective amount of 1-hydroxyethylidene-1,1-diphosphonic acid as a hydrogen peroxide stabilizer.

11. The method of claim 10, and further comprising adding an effective amount of glycerin.

5,607,698

13

12. The method of claim 11, wherein said glycerin is added in an amount from 0.005% to 0.1% by weight.

13. A method according to claim 1 wherein the active ingredient is diclofenac sodium.

14. A method according to claim 1 wherein the active ingredient is pilocarpine hydrochloride.

15. A method according to claim 1 wherein the active ingredient is tetrahydrozoline hydrochloride.

16. A method of treating the eye of a mammal in need of treatment with an ophthalmic drug which comprises directly instilling into the eye of a said mammal an effective amount of an ophthalmic drug formulation effectively preserved by trace amounts of stabilized hydrogen peroxide comprising

(a) an effective amount of an ophthalmic active ingredient which is compatible with hydrogen peroxide;

(b) a source of hydrogen peroxide for providing hydrogen peroxide in a trace amount from about 0.001% to about 0.01% by weight; and

(c) one or more ocularly compatible hydrogen peroxide stabilizers in sufficient amount to stabilize the hydrogen peroxide; said peroxide preserved ophthalmic drug formulation to be instilled directly in the eye of a mammal, having an ocularly compatible pH of between about 5.5 and about 8.0 and being substantially isotonic.

17. A method according to claim 16 wherein the active ingredient is naphazoline hydrochloride.

18. A method according to claim 16 wherein a said hydrogen peroxide source is selected from the group consisting of hydrogen peroxide, sodium perborate, sodium peroxide and urea peroxide, and a said hydrogen peroxide stabilizer is diethylene triamine penta(methylenephosphonic acid) or a 1-hydroxyethylidene-1,1-diphosphonic acid, or a physiologically compatible salt thereof.

19. A method according to claim 16 wherein said effective amount of diethylene triamine penta(methylenephosphonic acid), or a physiologically compatible salt thereof, is from 0.002% to 0.03% by weight and said effective amount of 1-hydroxyethylidene-1,1-diphosphonic acid or physiologically compatible salt thereof is from 0.005% to 0.2% by weight.

20. A method according to claim 16 further comprising an effective hydrogen peroxide stabilizing amount of glycerin.

14

21. A method according to claim 16 wherein the source of hydrogen peroxide is sodium perborate and the hydrogen peroxide stabilizer is diethylene triamine penta(methylenephosphonic acid).

22. A method according to claim 16 wherein the active ingredient is diclofenac sodium.

23. A method according to claim 16 wherein the active ingredient is pilocarpine hydrochloride.

24. A method according to claim 16 wherein the active ingredient is tetrahydrozoline hydrochloride.

25. A method of treating the eyes of a mammal by directly instilling into a said eyes in need of treatment an effective amount of an ocularly compatible eye wetting solution, eye lubrication solution or ophthalmic drug formulation which has been effectively preserved with a trace amount of stabilized hydrogen peroxide resulting from

(a) a source of hydrogen peroxide providing hydrogen peroxide in a trace amount from about 0.001% to about 0.01% by weight; and

(b) one or more ocularly compatible hydrogen peroxide stabilizers in sufficient amount to stabilize the hydrogen peroxide.

26. A method according to claim 25 wherein a said hydrogen peroxide source is selected from the group consisting of hydrogen peroxide, sodium perborate, sodium peroxide and urea peroxide, and a said hydrogen peroxide stabilizer is diethylene triamine penta(methylenephosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, or a physiologically compatible salt thereof.

27. A method according to claim 26 wherein said effective amount of diethylene triamine penta(methylenephosphonic acid), or a physiologically compatible salt thereof, is from 0.002% to 0.03% by weight and said effective amount of 1-hydroxyethylidene-1,1-diphosphonic acid or physiologically compatible salt thereof is from 0.005% to 0.2% by weight.

28. A method according to claim 27 wherein the source of hydrogen peroxide is sodium perborate and the hydrogen peroxide stabilizer is diethylene triamine penta(methylenephosphonic acid).

* * * * *

EXHIBIT B

US005725887A

United States Patent

[19]

[11] **Patent Number:** **5,725,887****Martin et al.**[45] **Date of Patent:** **Mar. 10, 1998**

[54] **METHOD OF PRESERVING OPHTHALMIC SOLUTIONS AND COMPOSITIONS THEREFOR**

[75] **Inventors:** **Stephen M. Martin, Roswell; Fu-Pao Tsao, Lawrenceville, both of Ga.**

[73] **Assignee:** **CIBA Vision Corporation, Duluth, Ga.**

[21] **Appl. No.:** **709,452**

[22] **Filed:** **Sep. 5, 1996**

Related U.S. Application Data

[63] Continuation of Ser. No. 339,447, Nov. 14, 1994, Pat. No. 5,607,698, which is a continuation of Ser. No. 99,986, Jul. 29, 1993, abandoned, which is a continuation of Ser. No. 968,224, Oct. 29, 1992, abandoned, which is a continuation of Ser. No. 733,485, Jul. 22, 1991, abandoned, which is a continuation of Ser. No. 376,083, Jul. 6, 1989, abandoned, which is a continuation-in-part of Ser. No. 229,163, Aug. 4, 1988, abandoned.

[51] **Int. Cl.⁶** **A61K 31/16**

[52] **U.S. Cl.** **424/613; 514/912**

[58] **Field of Search** **424/613; 514/912**

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,701,825 10/1972 Radimer et al. 423/273
4,051,058 9/1977 Böwing et al. 252/186.31
4,294,579 10/1981 Kowalski 8/111
4,304,762 12/1981 Leigh 423/272

4,347,149 8/1982 Smith et al. 252/102
4,350,681 9/1982 Fulton 424/53
4,614,646 9/1986 Christiansen 423/272
4,743,447 5/1988 Le Rouzie et al. 424/130
4,812,173 3/1989 Tsao et al. 423/272
4,889,689 12/1989 Tsao 422/30

FOREIGN PATENT DOCUMENTS

15818 9/1980 European Pat. Off. .
1382466 1/1975 United Kingdom .
1500702 2/1978 United Kingdom .

OTHER PUBLICATIONS

Kontaktlinsen—Chemic, Merian Verlag 1984, p. 173.
Contacto, International Contact Lens Journal, vol. 23, No. 1, Jan. 1979, pp. 37–40.
American Journal of Optometry and Physiological Optics, vol. 65, No. 2, pp. 91–98, Feb. 1988.

Primary Examiner—Zohreh Fay

Attorney, Agent, or Firm—Michael U. Lee; R. Scott Meece

[57] **ABSTRACT**

A preservative for ophthalmic solutions having an active ingredient is provided, having a hydrogen peroxide content of about 0.001% to about 0.10% by weight; and diethylene triamine penta(methylene phosphonic acid) or a physiologically compatible salt thereof, present at about 0.002% to 0.03% by weight and/or 0.005% to about 0.20% by weight of 1-hydroxyethylidene-1,1-diphosphonic acid, or physiologically acceptable salt thereof.

20 Claims, No Drawings

5,725,887

1

METHOD OF PRESERVING OPHTHALMIC SOLUTIONS AND COMPOSITIONS THEREFOR

This is a continuation of application No. 08/339,447 filed Nov. 14, 1994 now U.S. Pat. No. 5,607,698 which is a continuation of application No. 08/099,986 filed Jul. 29, 1993 now abandoned which is a continuation of application No. 07/968,224 filed Oct. 29, 1992 now abandoned which is a continuation of application No. 07/733,485 filed Jul. 22, 1991 now abandoned which is a continuation of application No. 07/376,083 filed Jul. 6, 1989 now abandoned which is a continuation in part of application No. 07/229,163 filed Aug. 4, 1988 now abandoned.

The present invention relates to a method of preserving ophthalmic solutions with trace amounts of stabilized peroxy compounds. More particularly, this invention relates to the use of stabilized trace amounts of hydrogen peroxide as preservative in buffered saline for eye care solutions.

Hydrogen peroxide is a well-known germicidal agent. For example, hydrogen peroxide in the form of a relatively dilute solution, e.g. about 0.5 to 6% by weight in water, is known to be effective as a disinfectant for use with contact lenses in order to kill any contaminating microorganisms.

One drawback with unstabilized dilute hydrogen peroxide solutions, however, is that without the use of a stabilizer or a combination of stabilizers, the aqueous peroxide solutions characteristically decompose over a period of time. The rate at which such dilute hydrogen peroxide solutions decompose will, of course, be dependent upon such factors as pH and the presence of trace amounts of various metal impurities, such as copper or chromium, which may act to catalytically decompose the same. Moreover, at moderately elevated temperatures, the rate of decomposition of such dilute aqueous hydrogen peroxide solutions is greatly accelerated.

A large variety of stabilizers have been proposed for use with hydrogen peroxide to deactivate trace catalytic impurities, including stannous salts, ethylene diamine tetra acetic acid, and the like. For example, U.S. Pat. No. 3,860,391 discloses bleaching compositions containing hydrogen peroxide and, as a stabilizer, amino lower alkylene phosphates, including diethylene triamine penta(methylene phosphonic acid) or salts thereof, and/or hydroxy alkane phosphates, with or without additional stabilizer constituents, and adjusted to a pH of between about 9.0 and 12.0 with, e.g. sodium hydroxide, for the bleaching of cellulosic materials. Exemplified are compositions having a pH of 12.0. However, such highly basic compositions are undesirable in ophthalmically-related solutions, including eyewashes and contact lens cleaning solutions.

Also, British Patent No. 1,500,707 discloses a contact lens sterilizing solution using hydrogen peroxide with 200-2000 ppm of a phosphate [pyrophosphate] stabilizer at a pH of 4.5.

However, the disinfection is not carried out at a pH consistent with the ocular environment since the pH needs to elevated to around 7. Also, the peroxide must be eliminated so as to make the solution compatible with the eye.

U.S. Pat. No. 4,304,762 discloses stabilization of aqueous hydrogen peroxide by addition of diethylenetriamine penta(methylene phosphonic acid) or a salt thereof at a pH of about 7. However, the stabilizing phosphonate compound is reported to be particularly effective for use with alkaline hydrogen peroxide solutions. Further these solutions are disclosed as being of use as a base for liquid bleach products. There is neither any hint that trace amounts of hydrogen

2

peroxide are effectively stabilized nor is there any indication that hydrogen peroxide might be used as a preservative for an ophthalmic solution.

Some of the eye care solutions commercially available today use benzalkonium chloride, rather than hydrogen peroxide, as a preservative. For example, contact lens solutions typically contain 0.9% sodium chloride, buffers, surfactants, wetting agents, and 0.002 to 0.01% benzalkonium chloride. Benzalkonium chloride is also used in other products, including isotonic decongestant ophthalmic solutions, such as Visine® eyedrops manufactured by the Leeming Division of Pfizer, Inc.

A problem exists, however, in that benzalkonium chloride, being cationic in character, reacts with proteins found in the ocular environment and causes unwanted deposits on soft contact lenses. Benzalkonium chloride and its analogs are also taken up by lens material and can have a deleterious effect on the structure of the lens [Davis, S. S. et al., "The Adsorption of Cationic Antimicrobial Agent Onto PolyHema", *Colloids and Surfaces*, 12, 203-212 (1984)]. In addition, benzalkonium chloride is inactivated by many compounds, including those associated with cotton and nylon fibers. Furthermore, in Swan, K. C., "Reactivity of the Ocular Tissues to Wetting Agents", *Am. J. Ophthalmol.*, 27, 118 (1944), it was noted that repeated use of benzalkonium chloride at concentrations of 1:5000 or stronger can denature the corneal protein and cause irreversible damage. It was also found that 0.04% to 0.05% solutions of benzalkonium chloride can cause superficial puncture disturbance of the corneal epithelium.

Other preservatives currently in use include thimerosal, which can cause a sensitivity reaction to the eye, and sorbic acid, which commonly causes lens discoloration. The disadvantages of the commonly used preservatives such as thimerosal, benzalkonium chloride and others are discussed in the following literature: M. Sibley, et al., "Understanding Sorbic Acid-Preserved Contact Lens Solutions", *International Contact Lens Clinic*, 11 (9), 531 (1984); M. Orron, et al., "Measurement of Preservative Binding with Soflens® (polymacon) Contact Lens", *Aust. J. Optom.*, 59, 277 (1976); and M. Akers, "Considerations in selecting antimicrobial preservative agents for parenteral product development", *Pharmaceutical Technology*, May, p. 36 (1984).

OBJECTS OF THE INVENTION

An object of the invention is to provide a preservative for all manner of ophthalmic and ophthalmically related solutions having hydrogen peroxide compatible components which does not suffer from the aforementioned defects.

Another object of the invention is to provide preserved ophthalmic and ophthalmically related solution formulations which are free of the known art preservatives.

Yet another object of the invention is to provide a means of preserving ophthalmic and ophthalmically related solutions with hydrogen peroxide or hydrogen peroxide generating components.

SUMMARY OF THE INVENTION

Surprisingly, the disadvantages of the prior art preservatives are overcome by stabilized trace peroxy compounds provided by the present invention which may be used as a preservative in ophthalmic solutions such as eye lubrication solutions, ophthalmic drug formulations and contact lens solutions.

The low levels of peroxy compounds are below the commercially suitable amounts necessary for the peroxy

5,725,887

3

compound to act as a disinfectant and is either low enough to be tolerable to direct application to the eye or may be made so by simple dilution with water or saline. In addition, the pH is also compatible with the ocular environment or upon the dilution indicated above is made so. For ophthalmic solutions (those which are to be instilled in the eye directly), the peroxy content and pH must per se be in the "ocular compatible range". Ophthalmic related solutions (those which are used in conjunction with contact lenses, other than "comfort or lubricating" drops which may be for instillation directly to the eye) may have appreciably higher peroxy content, but are intended to be diluted before being instilled in the eye or are used in such small amounts in the eye, that natural tear fluid dilution is sufficient to convert that solution to a solution which is compatible with the ocular environment.

The invention therefore relates to hydrogen peroxide or a source of hydrogen peroxide in trace amounts as a preservative for an ophthalmic solution, said hydrogen peroxide being especially effectively stabilized by addition of diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonate, to the use of said stabilized trace amounts of hydrogen peroxide for preserving an ophthalmic solution, to ophthalmic solutions so preserved, to the manufacture of so preserved ophthalmic solutions and to a method of preserving any ophthalmic solution by adding thereto said stabilized trace amounts of stabilized hydrogen peroxide or a source of hydrogen peroxide.

For example, the trace amount of the hydrogen peroxide in these ophthalmic solutions ranges from about 0.001% (10 ppm) to about 0.10% (1000 ppm) by weight and is stabilized by about 0.002% (20 ppm) to about 0.03% (300 ppm) by weight of diethylene triamine penta(methylene phosphonic acid) or a physiologically compatible salt thereof.

Alternatively or additionally from 0.005% to about 0.2% by weight of 1-hydroxyethylidene-1,1-diphosphonic acid and/or from about 0.005% to about 0.1% of glycerin can be added to the solution.

DETAILED DESCRIPTION OF THE INVENTION

Trace amounts of peroxy compounds stabilized with a hydrogen peroxide stabilizer, especially diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid may be utilized as a preservative for drugs, eyewashes, or other solutions containing an active ingredient designed to be used in the ocular environment. The preservative according to the present invention may be used in the ocular environment. The preservative according to the present invention may be used in any ophthalmic solution as long as the active ingredient in that solution is compatible with trace amounts of the peroxy compounds. Also, virtually any peroxy compound may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, cannot be stabilized utilizing the present system.

The full scope of the present invention includes ophthalmic active agent containing solutions as well as solutions which are ophthalmic active agent free. The former group contains at least one medicinal agent for application directly to the eye. The latter group comprises such solutions as

4

preserved saline, preserved contact lens cleaning solutions, preserved contact lens stabilizing solutions, preserved wetting solutions, and preserved lubricating solutions, among others.

It is believed that most compounds, when preserved by the present invention, are compatible with trace amounts of hydrogen peroxide. The following is a non-exhaustive, non-limiting, illustrative list of active ingredients and excipients that are compatible with the preservative according to the present invention: atropine, homatropine, cyclopentolate, tropicamide, lachesine, dibutoline, oxypheonium, eucatropine, ephedrine, carbachol, methacholine, pilocarpine hydrochloride, isofluorophate, physostigmine, neostigmine, lignocaine, cocaine, acetylcholine chloride, antazoline phosphate, betaxolol hydrochloride, demecarium bromide, dipivefrin hydrochloride, erythromycin, gentamicin sulfate, homatropine hydrobromide, idoxuridine, isosorbide, lanolin, naphazoline hydrochloride, neomycin sulfate, pheniramine maleate, polysorbate gelatin (Tween), pyrilamine maleate, scopalamine hydrobromide, hyaluronic acid, sodium hyaluronate, tetracaine hydrochloride, oxmetazolin, tetrahydrozoline hydrochloride, diclofenac sodium, dextran, carteolol, sulfanilamide, procaine, proparacaine hydrochloride, sulfisoxazole disulfonate, indomethacin, clonidine, corynanthine, arachidonic acid, linoleic acid, H-thymidine and 3H-thymidine, inositol triphosphate, inositol phosphates, phosphatidylinositol and phosphatidylinositol phosphates.

Excipients of various types compatible with the present invention include, but are not limited to:

Polysorbate gelatin (Tween)

Dextran

Linolin

Inositol phosphates

Alkylsulfosuccinates

Sulfosuccinamate

Alkyl Silicone Sulfosuccinates

Alkylpolyether carboxylates

Alkylaryl polyethoxylamines

Alkylarylsulfonates

Alpha Olefin sulfonates

Alkyl surfates

Alkyl ether sulfates

Alkanol amides and alkamides

Alkylamphoterics

Amphoterics based on Alkyl imidazoline

Betaines

Alkylaminopropionates

Alkyliminodipropionates

Alkylamphoglycinates

Alkylamphocarboxyglycinates

Alkylamphocarboxypropionates

Alkylamphopropionates

Alkylamidopropylhydroxysultaines

Alkyletherhydroxypropylsultaines

Alkylamphopropylsulfonates

Quaternary ammonium polymers

Quaternary ammonium halides

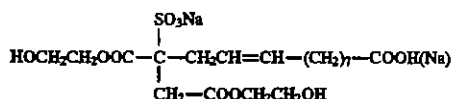
Polyacrylamide

Polyacrylates

5,725,887

5

Polyvinyl pyrrolidone
 Polyvinyl alcohol
 Alkylalcohol ethoxylates
 Hydroxyalkylcelluloses
 Alkylamidopropyl PG-Dimonium chloride phosphates
 Alkylampho PG-glycinate phosphates
 Glyceryl monoalkylates
 Sorbitan alkylates (span)
 Pluronics
 Tetronics
 Sodium alkyl sulfates
 Sodium Butoxyethoxy Acetate
 Phosphate esters
 Glycosides
 Polyglycosides
 Mannitol
 Sorbitol
 Polyoxyethylene alkyl ethers
 Grillosan having the formula

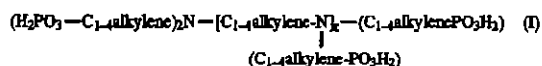


Guar gum
 Sodium hyaluronate
 Polyoxyl 40 stearate
 Polyoxyalkylene dimethylpolysiloxane

However, compounds having non-hindered hydroxyl groups attached to an aromatic ring, such as ketones and alcohols, or having a mercapto group, thioether, acetamido group, or aldehyde group will typically not be compatible. Such compounds believed not compatible with trace stabilized hydrogen peroxide include: noradrenaline, adrenaline, phenylephrine hydrochloride, amethocaine, oxybuprocaine, proxymethacaine, croimolyn sodium, benoxinate hydrochloride, chloramphenicol, chlortetracycline hydrochloride, dexamethasone, dichlorphenamide, echotiophate iodide, epinephrine bitartrate, fluorometholone, gramicidin, hydrocortisone, methazolamide, natamycin, prednisolone acetate, sulfacetamide (N¹-acetylsulfanilamide), tetracycline hydrochloride and timolol maleate.

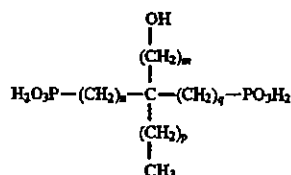
The peroxy stabilizer used in the present invention may be any of the known stabilizers of peroxy compounds including phosphates, phosphates, stannates, etc. However, physiologically compatible salts of phosphonic acids are preferred. Within this preferred group are

(a) compounds of the formula



wherein z is an integer of from 0-3; and (b) compounds of the formula

6



wherein each of n, m, p and q is independently 0-4, or physiologically compatible salts thereof. Highly preferred within formula I are compounds wherein z is 2 and compounds wherein each C₁₋₄ alkylene group is C₁ or C₂. Most preferred within formula I is diethylene triamine penta (methylene-phosphonic acid and the physiologically compatible salts thereof, marketed by Monsanto under the name Dequest® 2060. Highly preferred within formula II are compounds wherein n, m, p and q are each 0 or 1, most preferably zero, or a physiologically compatible salt thereof, marketed by Monsanto under the name Dequest® 2010.

Physiologically compatible salts of the compounds of formulae I and II include, for example, water soluble salts with conventional pharmaceutically acceptable cationic moieties, including the alkali metal, e.g. sodium, potassium, alkaline earth metal, e.g. calcium, ammonium and amine cations. Suitable amine salts include, for example, mono-, di-, and tri-lower alkyl amines, e.g. methylamine, ethylamine, diethylamine, triethylamine, dimethylamine, trimethylamine, propylamine, and the like; and mono-, di-, and tri-lower hydroxyalkyl amines, e.g. ethanolamine, diethanolamine, triethanolamine, glucamine, 2-hydroxypropylamine, and the like. By "lower" in the context of an alkyl group is meant an alkyl group having up to 6 carbon atoms, preferably up to 4 carbon atoms.

If desired, additional conventional stabilizers may be employed in conjunction with those of formulae I or II or combinations thereof in accordance with the present invention. Suitable conventional stabilizers include: water soluble stannates, such as an alkali metal or ammonium stannate, for example sodium stannate, alone or in combination with a water soluble phosphate, polyphosphate or etaphosphate salt, such as an alkali metal or ammonium salt thereof; or an amino polycarboxylic acid chelating agent, such as ethylene diamine tetraacetic acid, nitrilo triacetic acid or a water soluble salt thereof, such as an alkali metal or ammonium salt, especially the sodium salt, or mixtures thereof.

Still further peroxy stabilizers which may be used in the invention include a peroxide stabilizer selected from glycerin, polyvinyl alcohol having a molecular weight in the range of about 5,000 to about 150,000 (as long as water soluble) and being at least 80% hydrolyzed, propylene glycol, polyacrylic acid having a molecular weight of about 2,000 to about 100,000, diethylene glycol, and sodium hexamethaphosphate sodium polyphosphate (available from FMC under the name Hexaphos®).

The above stabilizers can be used in almost all indications previously mentioned to which the invention is applicable. However, when the solution is to come in contact with a hydrogel soft contact lens, stannate stabilizers are to be avoided as they tend to "cloud" the lens material.

Preferably, the concentration of the stabilizer of formula I or salt thereof is present in the stabilized composition in an amount between about 0.006 and about 0.02% by weight of the composition, and most preferably between about 0.006 and about 0.0120% by weight of the composition.

The stabilizer of formula II is present per 100 g of solution in an amount of at least about 0.024 m mole (50 ppm).

5,725,887

7

preferably 0.039 m mole (80 ppm) up to about 0.34 m mole (700 ppm) more preferably 0.049 m mole (100 ppm) up to about 0.29 m mole (600 ppm), most preferably 0.073 m mole (150 ppm) to about 0.19 m mole (400 ppm). The amounts in parentheses are for Dequest® 2010 which has a molecular weight of 206. Other stabilizers of formula II should be present in molar equivalents thereto.

The stabilizers other than those of formula I and II are employed in a physiologically tolerable amount, e.g. about 20 ppm to about 1000 ppm, preferably in an amount of at least 0.054 m mole (50 ppm), more preferably 0.087 m mole (80 ppm) to about 1.09 m mole (1000 ppm), still more preferably from about 0.109 m mole (100 ppm) to about 0.87 m mole (800 ppm), most preferably about 0.22 m mole (200 ppm) to about 0.65 m mole.

The pH of the stabilized solution is between about 5.5 and about 8. Preferably, the pH of the stabilized hydrogen peroxide solution is between about 6.0 and 8.0, most preferable between about 6.5 and 7.5. The pH can be adjusted as desired by incorporation of suitable amounts of acid or base of a physiologically tolerable nature in the amounts employed, e.g. hydrochloric acid and sodium hydroxide.

The pH of the stabilized solution presents another advantage over the prior art since the pH's of most existing ophthalmic solutions containing hydrogen peroxide are relatively low. The pH values of available hydrogen peroxide products for contact lenses are listed as follows:

Name of the Product	pH	% of H ₂ O ₂
AOSept (CIBA Vision)	6.3-6.6	3.3-3.5
Lensept (CIBA Vision)	3.98	3.4
Oxysept (Allergan)	3.28	3.3
Mirasept (Coopersvision)	3.96	3.6
Quiksept (Bausch & Lomb)	3.57	3.5
Puresept (Abbott Labs)	3.83	3.4
Softmate II (Barnes Hind)	3.5-3.6	3.5

Also, there may be present in the stabilized hydrogen peroxide solution according to the present invention one or more conventional, substantially inert, physiologically acceptable tonicity enhancing agents. Suitable such agents include, for example, alkali metal halides, phosphates, hydrogen phosphate, and borates. Preferred are sodium chloride, sodium phosphate monobasic and sodium phosphate dibasic. The function of such tonicity enhancing agents is to assure approximate physiologic tonicity to the solution which is instilled in the eye or to help assure such tonicity upon dilution if dilution is necessary prior to contact with the eye due to peroxide content as indicated above.

Preferably sufficient tonicity enhancing agents are present in the solution so that it is substantially isotonic or, such that, upon decomposition or dilution of the hydrogen peroxide therein, the resulting solution is substantially isotonic, e.g. substantially equivalent in tonicity to a 0.9% by weight aqueous sodium chloride solution.

A further optional ingredient is a thickener or viscosity enhancing agent. Any of the substances known in these categories which are ocularly acceptable can be used. Typical suitable thickeners include, inter alia, polyvinylalcohol, hydroxy ethylcellulose, etc. Thickeners may be present in any amount up to an amount sufficient to raise the overall solution viscosity to about 1000 cps, preferably to not more than 100 cps.

In general, the stabilized hydrogen peroxide solutions of the present invention are characterized by their extraordinary stability, even under accelerated conditions, for

8

example by heating the solutions to 100° C. for 24 hours. Thus, the shelf life of these compositions is enhanced. Moreover, the instant compositions are characterized by either physiological tolerability subsequent to hydrogen peroxide decomposition.

Another advantage in using hydrogen peroxide in ophthalmic solutions is that the trace amount of hydrogen peroxide, especially less than 100 ppm, is destroyed once comes in contact with the eye. For example, catalase existing in the eye tissue will cause the breakdown of the hydrogen peroxide into water and oxygen. As a result, the solution, upon application, becomes preservative free and greatly minimizes adverse reactions. The problems associated with other preservatives, such as the inability to break down innocuous compounds, are eliminated.

Formulation of the solutions of the invention can be made in any conventional manner. For example, all of the components other than the hydrogen peroxide and water can be placed in a container and fresh, preferably concentrated, hydrogen peroxide added thereto with mixing. Alternatively the dry components can be rubbed up with a small portion of liquid stabilizer, then the remainder of the stabilizer added, followed by the hydrogen peroxide, and most of the water. The viscosity enhancing agent, i.e. thickener, can then be added or the formed solution can be added to the thickener. One of ordinary skill in the art will be aware of numerous variations in the manner of formulating the solutions of the invention.

When it is desirable to "neutralize" the peroxide activity, any means known, such as rinsing, contacting the solution with platinum, catalase, or any other substance known to decompose hydrogen peroxide, will suffice. Additional physiological compatible peroxide neutralizing agents include reducing agent such as pyruvic acid and suitable salts thereof such as the sodium salt.

The following examples are presented for illustrative purposes and are not intended to limit the scope of this invention, but to demonstrate the stability of the peroxy solutions as stabilized in accordance with the present invention. All parts are by weight unless otherwise indicated.

EXAMPLE 1

Dissolve 0.610 g of sodium chloride, 0.005 g of sodium tetraborate, 10 H₂O, 0.5 g of boric acid, 0.006 g of diethylene triamine penta(methylene phosphoric acid) and 0.1 g of tetrahydrozoline hydrochloride in 80 ml of purified deionized water. Add 0.0225 g of sodium perborate, add water up to 100 ml and adjust the pH to 7 by the addition dropwise of dilute hydrochloric acid or sodium hydroxide. The resulting solution is then heated to 100° C. for a period of 24 hours. The solution possesses a "hot stability" of above 90%, which is the ratio of the hydrogen peroxide present in the after-heated sample to the before-heated sample, multiplied by 100[%].

EXAMPLE 2

The procedure of example 1 is duplicated, except that 0.1 g of sodium [o-[(2,6-dichlorophenyl)amino]phenyl]acetate replace the tetrahydrozoline hydrochloride. The hot stability is found to be 91.0%.

EXAMPLE 3

The procedure of example 1 is duplicated, except that 0.5 g of pilocarpine hydrochloride replace the tetrahydrozoline hydrochloride. The hot stability is found to be 74.3%.

5,725,887

9

EXAMPLE 4

The procedure of example 1 is duplicated, except that 0.1 g of naphazoline hydrochloride replace the tetrahydrozoline hydrochloride. The hot stability is found to be 81.3%.

EXAMPLE 5

Dissolve 0.61 g of sodium chloride, 0.50 g boric acid, 0.005 g of sodium borate decahydrate, 0.05 g Grillozan (from RITA), and 0.006 g diethylene triamine penta (methylene phosphonic acid) in 80 ml of deionized water. Add 0.0238 g sodium perborate. Add water up to 100 ml and adjust the pH to 7 by the addition dropwise of diluted hydrochloric acid or sodium hydroxide. The resulting solution is then heated to 100° C. for 24 hours. The hot stability of this solution is 93.1%.

EXAMPLE 6

The procedure of example 5 is duplicated except that the 0.05 g of Grillozan are replaced by 0.5 g propylene glycol. The hot stability of this solution is above 92%.

EXAMPLE 7

The procedure of example 5 is duplicated except that the 0.05 g of Grillozan are replaced by 0.5 g glycerin and an additional 0.01 g magnesium chloride. The hot stability of this solution is above 94%.

EXAMPLE 8

The procedure of example 5 is duplicated except that the 0.05 g of Grillozan are replaced by 0.1 g magnesium chloride. The hot stability of this solution is above 96%.

EXAMPLE 9

The procedure of example 5 is duplicated except that the 0.05 g of Grillozan are replaced by 0.5 g SIPEX EST-30 (sodium trideceth sulfate, CAS No. 68585-34-2, from Alcolac). The hot stability of this solution is above 92%.

EXAMPLE 10

The procedure of example 5 is duplicated except that the 0.05 g of Grillozan are replaced by 0.5 g Pluronic F-127 (BASF). The hot stability of this solution is above 93%.

EXAMPLE 11

Dissolve 0.35 g of sodium chloride, 0.35 g of potassium chloride, 0.58 g boric acid, 0.005 g sodium borate decahydrate and 0.006 g diethylene triamine penta(methylene phosphonic acid) in 80 ml of deionized water. Add 0.0238 g sodium perborate. Add water up to 100 ml and adjust the pH to 7 by the addition dropwise of diluted hydrochloric acid or sodium hydroxide. The hot stability of this solution is above 91%.

EXAMPLE 12

The procedure of example 11 is duplicated except that the 0.35 g of potassium chloride are replaced by 0.35 g of calcium chloride. The hot stability of this solution is above 93%.

EXAMPLE 13

The procedure of example 6 is duplicated except that the 0.5 g propylene glycol and 0.0238 g sodium perborate are

10

replaced by 1 g propylene glycol and 0.0476 g sodium perborate. The hot stability of this solution is above 98%.

EXAMPLE 14

The procedure of example 13 is duplicated except that the 1 g propylene glycol is replaced by 0.1 g of citric acid. The hot stability of this solution is above 94%.

EXAMPLE 15

Dissolve 0.61 g of sodium chloride, 0.50 g boric acid, 0.005 g sodium borate decahydrate and 0.006 g diethylene triamine penta(methylene phosphonic acid) in 80 ml of deionized water. Add 0.0133 g sodium peroxide (from Mallinckrodt Cat. No. 7864). Add water up to 100 ml and adjust the pH to 7 by the additional dropwise of diluted hydrochloric acid or sodium hydroxide. The hot stability of this solution is above 93%.

EXAMPLE 16

The procedure of example 15 is duplicated except that the 0.0133 g sodium peroxide are replaced by 0.0138 g of urea hydrogen peroxide (from Aldrich Cat. No. 28913-2). The hot stability of this solution is above 53.6%.

EXAMPLE 17

Dissolve 0.61 g of sodium chloride, 0.50 g boric acid, 0.005 g sodium borate decahydrate, 0.1 g sulfanilamide (Sigma Cat. No. S-9251) and 0.006 g diethylene triamine penta(methylene phosphonic acid) in 80 ml of deionized water. Add 0.0238 g sodium perborate. Add water up to 100 ml and adjust the pH to 7 by the addition dropwise of diluted hydrochloric acid or sodium hydroxide. The hot stability of this solution is above 92%.

EXAMPLE 18

Dissolve 0.61 g of sodium chloride, 0.50 g boric acid, 0.005 g sodium borate decahydrate, and various amounts of 1-hydroxyethylidene-1,1-diphosphonic acid in 80 ml of deionized water. Add 0.0238 g sodium perborate. Add water up to 100 ml and adjust the pH to 7 by the addition dropwise of diluted hydrochloric acid or sodium hydroxide. The hot stabilities of those solutions are listed as follows:

1-Hydroxyethylidene-1,1-diphosphonic acid (g)	Hot Stability %
0.03	87.1
0.05	90.3
0.08	96.8

EXAMPLE 19

This is an example of 1-hydroxyethylidene-1,1-diphosphonic acid as a stabilizer. The procedure of example 18 is duplicated except that various amounts of glycerin are added. The hot stabilities of these solutions are listed as follows:

5,725.887

11

1-Hydroxyethylidene- 1,1-diphosphonic acid (g)	Glycerin (g)	Hot Stability %
0.03	0.03	90.3
0.05	0.03	93.5
0.08	0.03	93.5
0.03	0.05	90.3
0.05	0.05	90.3
0.08	0.05	93.5

EXAMPLE 20

The procedure of example 17 is duplicated except that the 0.1 g sulfanilamide are replaced by 0.1 g hyaluronic acid (from *Streptococcus Zooepidermicus*). The hot stability of this solution is about 86%.

EXAMPLE 21

The procedure of example 20 is duplicated except that the 0.1 g hyaluronic acid (from *Streptococcus Zooepidermicus*) are replaced by 0.1 g hyaluronic acid (from Rooster Comb.). The hot stability of this solution is above 96%.

EXAMPLE 22

The procedure of example 20 is duplicated except that the 0.1 g hyaluronic acid are replaced by 0.1 g sodium hyaluronate. The hot stability of this solution is above 92%.

EXAMPLE 23

The procedure of example 22 is duplicated except that the 0.1 g sodium hyaluronate are replaced by 0.025 g oxymetazoline. The hot stability of this solution is above 87%.

EXAMPLE 24

Microbial preservative effectiveness test results of 50 ppm hydrogen peroxide in a borate buffer are listed as follows:

PRESERVATIVE EFFECTIVENESS TEST (50 ppm H₂O₂ solution)

Challenge Microbe	Original Inoculum	Day 7	Day 14	Rechallenge on Day 14 with Inoculum
<i>E. coli</i>	1.67×10^6	Zero	Zero	1.60×10^8
<i>P. aeruginosa</i>	2.04×10^6	Zero	Zero	1.94×10^8
<i>S. aureus</i>	1.09×10^6	1.75×10^2	Zero	1.74×10^8
<i>A. niger</i>	1.46×10^5	2.15×10^4	8.40×10^3	1.00×10^8
<i>C. albicans</i> No. 1	1.63×10^6	8.00×10^2	2.40×10^2	1.41×10^8
<i>C. albicans</i> No. 2	1.63×10^6	1.35×10^2	3.40×10^2	1.41×10^8
<i>C. albicans</i> No. 3	1.63×10^6	1.75×10^2	4.90×10^2	1.41×10^8

Challenge Microbe	Day 21	Day 28	% Reduction	Pass/Fail
<i>E. coli</i>	Zero	Zero	100%	Pass
<i>P. aeruginosa</i>	Zero	Zero	100%	Pass
<i>S. aureus</i>	Zero	Zero	100%	Pass
<i>A. niger</i>	4.65×10^4	4.50×10^4		Pass
<i>C. albicans</i> No. 1	1.09×10^5	3.90×10^4		Pass
<i>C. albicans</i> No. 2	1.12×10^5	3.55×10^4		Pass
<i>C. albicans</i> No. 3	1.26×10^5	3.40×10^4		Pass

What is claimed is:

1. A preserved ophthalmic formulation comprising an eye wetting solution, an eye lubricating solution or comfort solution, or an ophthalmic drug formulation comprising an ophthalmic active agent which is compatible with hydrogen

12

peroxide, any said formulation being effectively preserved by an ocularly compatible amount of stabilized hydrogen peroxide generated from

(a) a source of hydrogen peroxide in sufficient amount to provide hydrogen peroxide in a trace amount from about 10 ppm to 100 ppm; and

(b) one or more ocularly compatible hydrogen peroxide stabilizers in a sufficient amount to stabilize the resultant hydrogen peroxide; the said preserved ophthalmic formulation being suitable to be directly instilled in the eye of a mammal.

2. A preserved ophthalmic formulation according to claim 1 wherein the hydrogen peroxide is provided in a trace amount of 10 to 80 ppm.

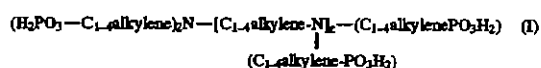
3. A preserved ophthalmic formulation according to claim 1 wherein the hydrogen peroxide is provided in a trace amount from 10 to 60 ppm.

4. A preserved ophthalmic formulation according to claims 1 wherein said source of hydrogen peroxide is hydrogen peroxide, sodium perborate, sodium peroxide or urea peroxide.

5. A preserved ophthalmic formulation according to claim 1 wherein said source of hydrogen peroxide is sodium perborate.

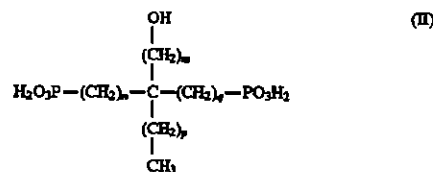
6. A preserved ophthalmic formulation according to claim 1 wherein the hydrogen peroxide stabilizer is selected from the group consisting of

(a) compounds of the formula



wherein z is an integer of from 0-3, and physiologically compatible salts thereof; and

(b) compounds of the formula



wherein each of n, m, p and q is independently 0-4, and physiologically compatible salts thereof.

7. A preserved ophthalmic formulation according to claim 6 wherein in formula I, z is 2 and each of C₁₋₄alkylene is C₁ or C₂; and wherein in formula II each of n, m, p and q is 0 or 1.

8. A preserved ophthalmic formulation according to claim 1 wherein a said hydrogen peroxide source is selected from the group consisting of hydrogen peroxide, sodium perborate, sodium peroxide and urea peroxide, and a said hydrogen peroxide stabilizer is diethylene triamine penta(methylenephosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, or a physiologically compatible salt thereof.

9. A preserved ophthalmic formulation according to claim 1 wherein said effective amount of diethylene triamine penta(methylenephosphonic acid) or physiologically compatible salt thereof, is from 0.002% to 0.03% by weight, and said effective amount of 1-hydroxyethylidene-1,1-diphosphonic acid or physiologically compatible salt thereof is from 0.005% to 0.2% by weight.

10. A preserved ophthalmic formulation according to claim 9 wherein the source of hydrogen peroxide is sodium

5,725,887

13

perborate and the hydrogen peroxide stabilizer is diethylene triamine penta(methylenephosphonic acid).

11. A preserved ophthalmic drug formulation according to claim 1 comprising

- (a) an effective amount of an ophthalmic medicinal agent which is compatible with hydrogen peroxide;
- (b) a source of hydrogen peroxide for providing hydrogen peroxide in a trace amount of about 10 to 100 ppm;
- (c) one or more ocularly compatible hydrogen peroxide stabilizers in sufficient amount to stabilize the hydrogen peroxide; said formulation to be applied directly to the eye of a mammal, having an ocularly compatible pH of between about 5.5 and 8.0 and being substantially isotonic.

12. A preserved ophthalmic drug formulation according to claim 11 wherein the hydrogen peroxide is provided in a trace amount of 10 to 60 ppm.

13. A preserved ophthalmic drug formulation according to claim 11 wherein a said hydrogen peroxide source is selected from the group consisting of hydrogen peroxide, sodium perborate, sodium peroxide and urea peroxide, and a said hydrogen peroxide stabilizer is diethylene triamine penta(methylenephosphonic acid) or a 1-hydroxyethylidene-1,1-diphosphonic acid, or a physiologically compatible salt thereof.

14. A preserved ophthalmic drug formulation according to claim 11 wherein said effective amount of diethylene tri-

14

amine penta(methylenephosphonic acid), or a physiologically compatible salt thereof, is from 0.002% to 0.03% by weight and said effective amount of 1-hydroxyethylidene-1,1-diphosphonic acid or physiologically compatible salt thereof is from 0.005% to 0.2% by weight.

15. A preserved ophthalmic drug formulation according to claim 11 wherein the source of hydrogen peroxide is sodium perborate and the hydrogen peroxide stabilizer is diethylene triamine penta(methylenephosphonic acid).

16. A preserved ophthalmic drug formulation according to claim 11 wherein the medicinal agent is diclofenac sodium.

17. A preserved ophthalmic drug formulation according to claim 11 wherein the medicinal agent is naphazoline hydrochloride.

18. A preserved ophthalmic drug formulation according to claim 11 wherein the medicinal agent is pilocarpine hydrochloride.

19. A preserved ophthalmic drug formulation according to claim 11 wherein the medicinal agent is tetrahydrozoline hydrochloride.

20. A preserved ophthalmic drug formulation according to claim 11 wherein the medicinal agent is naphazoline hydrochloride.

* * * * *